REMARKS

Claims 7, 9, 10, 12 are pending. Claim 7 has been amended to further recite that there is no target nucleic acid in the claimed composition. Support for the amendment can be found throughout the specification, *e.g.*, page 4, lines 14-15 and page 5, lines 24-36. Claim 11 has been cancelled without prejudice or disclaimer. Claim 7 has also been amended to change "the target sequence" to "said target nucleic acid" so as to be consistent with its antecedent basis. Claim 12 has been amended to remove dependency on cancelled claim 11. No new matter has been introduced by way of these amendments.

Rejection under 35 U.S.C. § 102(b)

Claims 7 and 9-12 stand rejected under 35 U.S.C. § 102(b) as anticipated by *Nilsson* (Science 265:2085-2088 (1994)). In particular, the Examiner alleges that the reference teaches the same composition for targeting nucleic acids, comprising a padlock probe having two free nucleic acid end parts that are partially complementary to and hybridize with neighboring regions of a target nucleic acid. The Examiner also contends that Nilsson's disclosure of a ligation buffer constitutes "a pharmaceutically acceptable carrier" as presently claimed. The Examiner supports this contention by citing additional references (*Rajagopalan*, *Shelley*, *Mills*, and *Rapaport*) for the proposition that the ligation buffer in *Nilsson* is inherently a pharmaceutically acceptable buffer.

Prior to addressing this specific rejection, it should be noted that Applicant has amended independent claim 7 to further distinguish *Nilsson*. The disclosure in *Nilsson*, relied upon by the Examiner, involves contacting the target nucleic acid/padlock probe duplex with ligation buffer. The present claim states that the target nucleic acid is not present in the claimed composition. As amended, claim 7 cannot be read upon the disclosure of *Nilsson*. On this basis alone the rejection should be withdrawn.

Regarding the above rejection, the cited reference is directed to the detection of nucleotide sequences using a circularizable probe. The probes are composed of two target-complementary sequences that are brought into juxtaposition by hybridization to a single stranded target sequence. In particular, Figure 4 (to which the Examiner has cited) discloses the use of the probe to detect DNA that has been denatured for *in situ* hybridization. In contrast, the present claims are directed to a composition for targeting double stranded nucleic acids

comprising a pharmaceutically acceptable carrier and an effective amount of a padlock probe oligonucleotide. As amended, the composition does not contain the target nucleic acid.

The Examiner contends that the ligation buffer used in these experiments constitutes a pharmaceutically acceptable carrier despite the fact that the figure illustrates experiments performed *in vitro*. In addition, there is no suggestion in the reference that the buffer, used as a wash after an 18-hour hybridization and subsequent ligation with the addition to T4 DNA ligase, could be used as a pharmaceutically acceptable carrier.

When the cited reference is silent about an alleged inherent characteristic, the gap in the reference may be filled with extrinsic evidence, such extrinsic evidence, though, must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. v. Monsanto*, 20 USPQ2d 1746, 1748 (Fed. Cir. 1991). Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Oelrich*, 212 USPQ 323, 326 (CCPA 1981) (quoting *Hansgirg v. Kemmer*, 40 USPQ 665, 667 (CCPA 1939)).

Here, the Examiner has cited four additional references, each teaching an individual component of Nilsson's ligation buffer as a pharmaceutically acceptable carrier. None of these references, however, disclose the actual ligation buffer as a pharmaceutically acceptable carrier. Thus, the references do not make clear that Nilsson's ligation buffer is known in the art as a pharmaceutically acceptable carrier. By analogy to *Oelrich*, it is not sufficient to show inherency simply because individual components of Nilsson's ligation buffer are disclosed in each of the four references as one of a multiplicity of other molecules that can be used as pharmaceutically acceptable carriers. It was not known in the art that the Nilsson's ligation buffer was inherently a pharmaceutically acceptable carrier because the Examiner has relied upon separate references for each component of the buffer, instead of one reference that states that Nilsson's ligation buffer is a pharmaceutically acceptable carrier.

Accordingly, Applicants submit that *Nilsson* does not anticipate the present claims because the reference does not teach the pharmaceutically acceptable carrier as claimed in the instant invention. Also, *Nilsson* does not disclose the claimed composition where the target nucleic acid is *not* present. Applicants respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first and second paragraphs

Claims 11 and 12 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. Claims 11 and 12 also stand rejected under § 112, first paragraph as failing to comply with the written description requirement. Applicants have cancelled claim 11 and amended claim 12 to remove its dependency on cancelled claim 11, thus rendering the rejections moot.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
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Dated: Dec 1, 2003

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Filed under 37 C.F.R. § 1.34(a)

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